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MECHANISM OF THE ATTENUATED CARDIAC RESPONSE TO BETA-ADRENERGIC--ETC(U)
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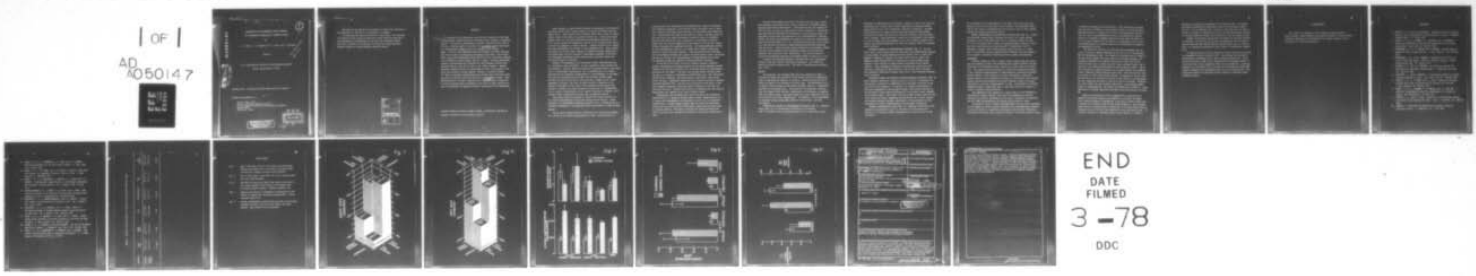

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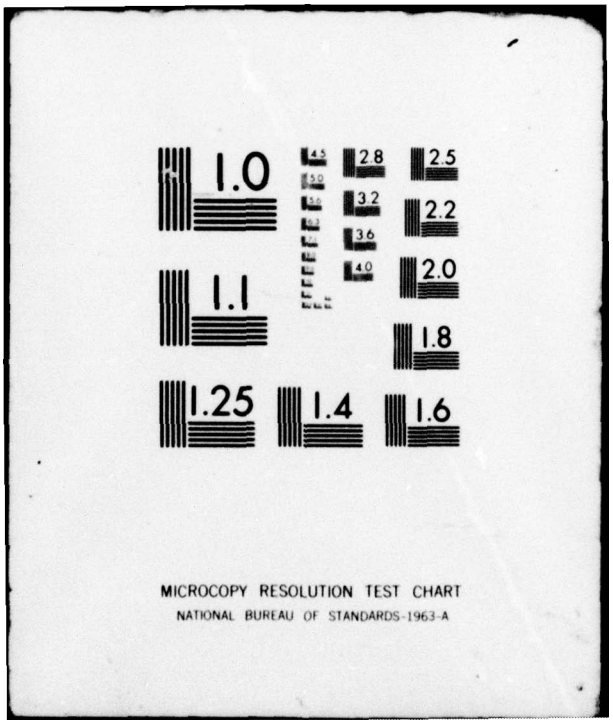
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B.S.

MECHANISM OF THE ATTENUATED CARDIAC RESPONSE TO β-ADRENERGIC STIMULATION IN CHRONIC HYPOXIA

by

J. T. Maher, J. C. Denniston, D. L. Wolfe, and A. Cymerman

see back page for 1473

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Running Title: Attenuated Cardiac Responsiveness in Hypoxia

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The views of the authors do not purport to reflect the positions of the Department of the Army or the Department of Defense.

In conducting the research described in this report, the investigators adhered to the 'Guide for Laboratory Animal Facilities and Care', as promulgated by the Committee on the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Academy of Sciences-National Research Council.

B.

ABSTRACT

A blunting of the chronotropic and inotropic responses of the heart to β-adrenergic stimulation occurs following chronic exposure to hypobaric hypoxia. To pursue the mechanism(s) involved, observations were made in 6 intact, conscious goats at sea level and in another 6 goats maintained in a decompression chamber at 445 torr (~4,300 m) for 10 days. ($\bar{P}_aO_2$ = 43 torr). No significant group differences in cardiac frequency and various indices of myocardial performance (peak dP/dt, time-to-peak dP/dt, V_{max}) were demonstrable either before or after cholinergic blockade with intravenous atropine methyl bromide, 1 mg/kg. Following hemodynamic studies, thoracotomies were performed and full-thickness biopsies were obtained from the free wall of each of the cardiac chambers. Neither monoamine oxidase activity nor norepinephrine level of any region of the heart was altered by chronic hypoxia. However, a twofold increase ($P < .001$) in catechol O-methyltransferase activity above sea-level values was found in both the atria and ventricles of the hypoxic animals. Thus, the attenuation in cardiac responsiveness to β-adrenoceptor stimulation in chronic hypoxia appears unrelated to the level of vagal activity, but may be attributable to enhanced enzymatic inactivation of catecholamines.

normoxia; hypobaric hypoxia; vagal blockade; catecholamine degradative enzymes; chronotropic and inotropic responses

Acute exposure to high altitude produces an adrenergic activation with increases in heart rate, cardiac output, and urinary and plasma catecholamines (17,3). After several days of hypoxia heart rate returns to, while cardiac output falls below, pre-exposure values (17). Since these latter changes occur at a time when circulating catecholamines continue to rise (12), one may assume that sympathetic control of the cardiovascular system is altered by exposure to chronic hypoxia. Previous studies in our laboratory have established the validity of this assumption (13). These studies have shown that several days' exposure to hypobaric hypoxia reduces both the chronotropic (13) and inotropic (unpublished) responses of the heart to β-adrenergic stimulation (with isoproterenol) and hence reduces the functional reserve of the heart.

However, the mechanism of the attenuated cardiac responsiveness has not, heretofore, been elucidated. In this connection, three factors must be considered. Firstly, chronic hypoxia may be associated with a more rapid rate of catecholamine inactivation. The two enzymes that are of major importance in the metabolic transformation of catecholamines in the mammal are catechol O-methyltransferase (COMT) and monoamine oxidase (MAO). Secondly, chronic hypoxia may be associated with a higher level of parasympathetic activity. The level of vagal activity in hypoxia can be assessed by blockade of this limb of the autonomic nervous system with atropine. Finally, one cannot exclude the possibility of a hyposensitivity or relative refractoriness of the cardiac β-receptors secondary to the elevated level of sympathetic activity that accompanies hypoxia.

The present study was designed to identify the causal factor(s) in the reduced responsiveness of the heart during chronic hypoxia. Understanding of the mechanisms responsible appeared to be a valuable basis for subsequent management of the depressed cardiac performance at high altitude.

METHODS

Twelve healthy domestic goats, conditioned for 3 months and weighing 25 to 30 kg, were studied in two groups of 6 each. Two weeks prior to

study the goats were anesthetized with pentobarbital sodium and catheters were implanted surgically in the carotid artery and jugular vein to facilitate pressure recordings, blood sampling, and intravenous drug administration. Observations were made in both groups of intact, conscious goats at sea level and in one group following 10 continuous days in a hypobaric chamber maintained at 445 torr, equivalent to an elevation of 4,300 m. Temperature and relative humidity were maintained at 21°C and 50%, respectively, throughout the experimental period. Following hemodynamic studies in each environmental condition, the animals were rendered unconscious using the captive bolt gun technique. Left thoracotomies were performed and full-thickness biopsies were rapidly obtained from the atria, ventricles and apex of the heart for determinations of norepinephrine (NE) levels, and monamine oxidase and catechol O-methyltransferase activities.

On the day of the study a micro-tip catheter pressure transducer (Millar Instruments) was inserted through the previously implanted carotid catheter into the left ventricle and a 3-lead ECG system was appropriately positioned on the animal. The goats were studied without sedation while resting in a stanchion. Measurements included heart rate; left ventricular end-diastolic, developed, and peak pressures; peak dP/dt; time-to-peak dP/dt; and V_{max}. Hemodynamic parameters were assessed according to methods described elsewhere (19). The data were collected in real-time by a PDP 11/40 computer, analyzed, stored and results returned in real-time via printouts and plots. Analyses were based on 15 cardiac cycles and pressure measurements were sampled at the rate of 500 per second.

Measurements were obtained before and 10 min after the intravenous administration of 1 mg/kg of atropine methyl bromide (Sigma Chemical Co.) to assess the parasympathetic contribution to heart rate and myocardial contractility. Atropine methyl bromide does not cross the blood-brain barrier and was used to avoid the CNS effects associated with high doses of atropine sulfate. This dose of atropine was tested previously and found to produce total blockade of the vagus to electrical stimulation in goats.

Arterial blood samples were drawn for analyses of P_{O2}, P_{CO2}, and pH with Radiometer electrodes and for oxygen saturation by oximetry (Instrumentation Laboratories CO-Oximeter). Blood gases and pH were measured at 37°C and later corrected to each animal's rectal temperature. Hematocrits were determined by high-speed centrifugation in microcapillary tubes, and hemoglobin concentration was measured by the cyanmethemoglobin technique. Cardiac and plasma norepinephrine were quantitated using the radioenzymatic assay described by Henry et al. (8) with minor modifications in the incubation time (90 min) and amount of phenylethanolamine-N-methyltransferase used (86 units). Tissue catechol O-methyltransferase and monoamine oxidase activities were measured by the radiometric methods of Griffiths and Linklater (6) and Jarrott (10), respectively. The protein content of tissues was determined using the Folin phenol method of Lowry et al. (11).

A subject-by-treatment analysis of variance and, where appropriate, Student t-test were used for statistical evaluation. All values are reported as mean ± standard error. The level of significance was chosen as $P < 0.05$.

RESULTS

The blood gas, pH, and hematologic data are presented in Table 1. Arterial O2 tension and saturation of the hypoxic group were dramatically lower during hypobaric hypoxia, as expected. Animals hyperventilated at 4,300 m as shown by the decrease in arterial P_{CO2}. The maintenance of pH at normoxic levels during chronic hypoxia probably reflects a compensatory excretion of bicarbonate ions. The hematocrit and hemoglobin concentration were higher by 28% and 24%, respectively, in the hypoxic as compared with the normoxic goats. Mean body weights and rectal temperatures of the two groups did not differ significantly. No difference in any measurement was observed between groups when studied in the normoxic, sea-level environment.

Chronotropic response to parasympathetic blockade (*Fig. 1*). Baseline heart rates were not significantly different in the normoxic (102 ± 9 beats/min) and chronically hypoxic (117 ± 7 beats/min) groups.

Following the administration of atropine, 1 mg/kg iv, heart rates rose significantly, but to values that were not significantly different between groups (151 ± 10 vs. 147 ± 6 beats/min, normoxia vs. hypoxia). Assuming total blockade of the vagus in both conditions (normoxia and hypoxia), differences in heart rate would have reflected different levels of sympathetic activity. Since group heart rates were not dissimilar either before or after atropine, nor was sympathetic tone, the conclusion appears inescapable that chronic hypoxia did not alter the normoxic level of parasympathetic activity.

Inotropic response to parasympathetic blockade (Fig. 2). As with heart rates, post-atropine values of peak dP/dt were significantly elevated in both groups, but group differences before (2916 ± 342 vs. 3269 ± 270 mmHg/sec, normoxia vs. hypoxia) and after (3668 ± 493 vs. 3925 ± 369 mmHg/sec) vagal blockade were not significant, thereby adding further support to the constancy of vagal activity following chronic hypoxic exposure. Other hemodynamic parameters including left ventricular end-diastolic, developed and peak pressures; time-to-peak dP/dt; and V_{max} were similarly unaffected by hypoxia both prior to and following parasympathetic blockade.

Monoamine oxidase and catechol O-methyltransferase activities (Fig. 3). While regional differences in MAO activity of the heart are apparent for both groups of animals, no significant group difference was found in any of the five areas examined. In contrast, the regional distribution of COMT was unremarkable in both groups although a very marked elevation in the activity of this enzyme was observed for each cardiac region examined in the hypoxic goats. The overall increase in COMT activity above the sea-level value was twofold, suggesting the possibility of a causal relationship between enhanced enzymatic inactivation of catecholamines and the attenuation in cardiac responsiveness to β-adrenergic stimulation.

Cardiac norepinephrine stores (Fig. 4). Regional differences in the endogenous norepinephrine levels of the hearts of both groups were apparent with strikingly higher concentrations in the atria than in the ventricles.

The concentration of norepinephrine in the right side of the heart was similar to that in the left side for both groups. No significant difference in the levels of norepinephrine was observed in any of these regions between the normoxic and hypoxic animals.

Plasma norepinephrine concentrations and heart rate (*Fig.* 5). Plasma norepinephrine concentration increased from 0.64 ± 0.13 ηg/ml during normoxia to 0.76 ± 0.04 ηg/ml after 24 h of hypobaric hypoxia and then to 1.25 ± 0.16 ηg/ml after 10 days of continuous hypoxic exposure. Heart rate also rose with acute hypoxia from 102 ± 9 beats/min to 131 ± 8 beats/min. However, with chronic hypoxia, heart rate fell to a value (117 ± 7 beats/min) that was insignificantly different from the normoxic value despite a concurrent twofold increase in plasma norepinephrine.

DISCUSSION

Previous studies in intact, lightly sedated mongrel dogs have shown that the increase in heart rate following isoproterenol injection was significantly less following 10 days' exposure at 4,300 m than at sea level (13). The present study was designed to explore the mechanisms operative in the attenuated responsiveness to sympathomimetic stimulation following chronic hypoxia. Pilot studies in the goat established a similarity between species in the chronotropic response to isoproterenol after chronic hypoxic exposure and extended the previous findings in dogs to include a depression in inotropic responsiveness, as well. An advantage of studying conditioned goats, unlike dogs (16), is that they need not be sedated to achieve a perfect resting situation.

The magnitude of the response of a target organ to catecholamines is determined by several factors: the level of parasympathetic activity opposing the stimulus, the ability of the organ to inactivate the material, and the number and sensitivity of receptor sites within the organ.

The relative level of cardiac parasympathetic activity can be estimated by the changes in several cardiac parameters after parasympathetic blockade. As the data indicate, significant chronotropic and inotropic differences occurred in both groups after atropine treatment, but chronic hypoxia failed

to produce any change in that difference. This observation indicates that the lack of response to the increased levels of circulating NE is probably not due to a change in the level of parasympathetic activity. That the level of parasympathetic activity can change with altitude exposure in response to maximal exercise has been shown by others (7). But our results suggest that the return of resting heart rate of altitude-exposed goats to sea-level values is not influenced by changes in parasympathetic activity.

The ability of the heart to inactivate NE is dependent upon the status of neuronal uptake mechanisms and the activity of intraneuronal MAO and extraneuronal COMT. Our finding of increased levels of COMT in the goat heart supports the thesis that the attenuated response to β-adrenergic stimulation we reported previously in dogs (13) and the return of heart rate to normal sea-level values reported herein, may be related to the enhanced inactivation of circulating NE by COMT . NE in the circulation is rendered inactive by the rapid uptake into peripheral stores, especially those within the heart (18). That this may not occur to as great an extent with chronic hypoxia is evidenced by the fact that MAO activity is not altered in the face of high levels of circulating NE and that endogenous NE levels in the heart are not increased. Exogenous NE, after uptake into the isolated canine heart, is principally metabolized to normetanephrine, the result of O-methylation by COMT (2). Thus, COMT may be of greater importance than MAO in the inactivation of cardiac NE.

Bassett and Cairncross (1) have suggested that repeated stress induced by footshock results in an inhibition of neuronal NE uptake. Their results indicate an interference in the rate of uptake rather than a change in the affinity of NE for the uptake mechanism. They interpret their results as demonstrating a competition for the same uptake sites by compounds such as steroids, thus reducing the sites available for NE. If a similar mechanism is operative during chronic hypoxia, it would be

expected to increase the availability of extraneuronal NE. An increase in substrate availability could thus account for an increase in COMT activity. It is noteworthy that a variety of steroids have been shown to inhibit the uptake of cardiac NE in the rat (9) and that hypoxia is known to increase plasma and urinary corticosteroids in man and animals (4,15).

Changes in NE receptor sensitivity and number are extremely difficult to determine. Our data do not exclude the possibility that the cardiac response observed with chronic altitude exposure may be due, at least in part, to a decrease in sensitivity and/or number of postsynaptic receptor sites.

It appears that the initial response to hypoxia results in a decrease in endogenous NE levels in heart (5,14). This decrease was blocked by hexamethonium, indicating that it may be reflexly mediated (5). After this initial phase, which is also characterized by increased turnover of cardiac NE (14), normal endogenous levels are re-established. Long-term adaptation is associated with an increase in the degradative enzyme COMT, probably induced by the persistently high level of circulating NE. This change may explain the attenuated cardiac response to exogenous sympathomimetic amines.

ACKNOWLEDGMENTS

The authors are indebted to Ellen Beekman, Richard Langevin, Adrien Lussier, Joanne Cardillo and Deborah Richardson for their skilled technical assistance; to John Marseglia for computer support; and to Ella Munro for statistical guidance.

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TABLE 1. Arterial blood analyses in normoxic and chronically hypoxic goats

CONDITION	Pa_{O_2} torr	Pa_{CO_2} torr	pHa	O_2 Saturation	Hct %	Hb g/100 ml
NORMOXIA	98.2 ± 1.6	39.0 ± 2.5	7.47 ± 0.01	94.9 ± 0.2	29.3 ± 1.2	10.2 ± 0.5
CHRONIC HYPOXIA	42.6 ± 2.0	31.2 ± 1.6	7.48 ± 0.02	78.8 ± 1.9	37.4 ± 1.7	12.6 ± 0.6
P	< 0.001	< 0.05	NS	< 0.001	< 0.01	< 0.01

FIGURE LEGEND

Fig. 1 Mean (± SE) heart rates of the normoxic and chronically hypoxic goats before and 10 min after intravenous administration of 1 mg/kg of atropine methyl bromide.

Fig. 2 Mean (± SE) values of peak dP/dt for the two groups before and after vagal blockade.

Fig. 3 Mean MAO (top panel) and COMT (lower panel) activities of the various regions of the hearts of the normoxic and chronically hypoxic animals. Brackets indicate 1 SE.

Fig. 4 Regional distribution of endogenous norepinephrine in the hearts of normoxic and chronically hypoxic goats. Values represent means ± SE.

Fig. 5 Plasma norepinephrine concentrations and heart rates during normoxia and after acute (24 h) and chronic (10 days) hypoxia. Mean values ± SE are presented.

Fig. 1

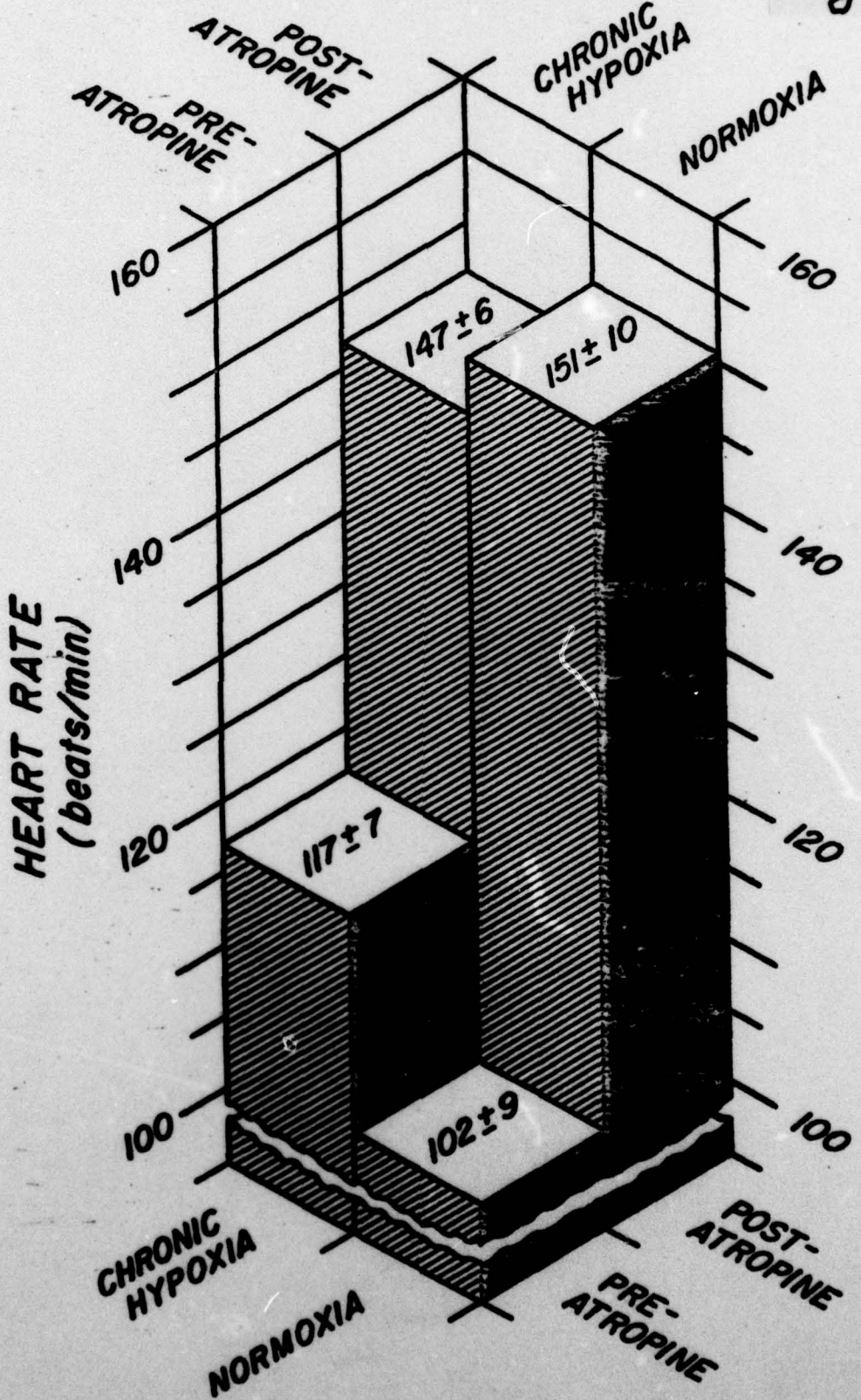
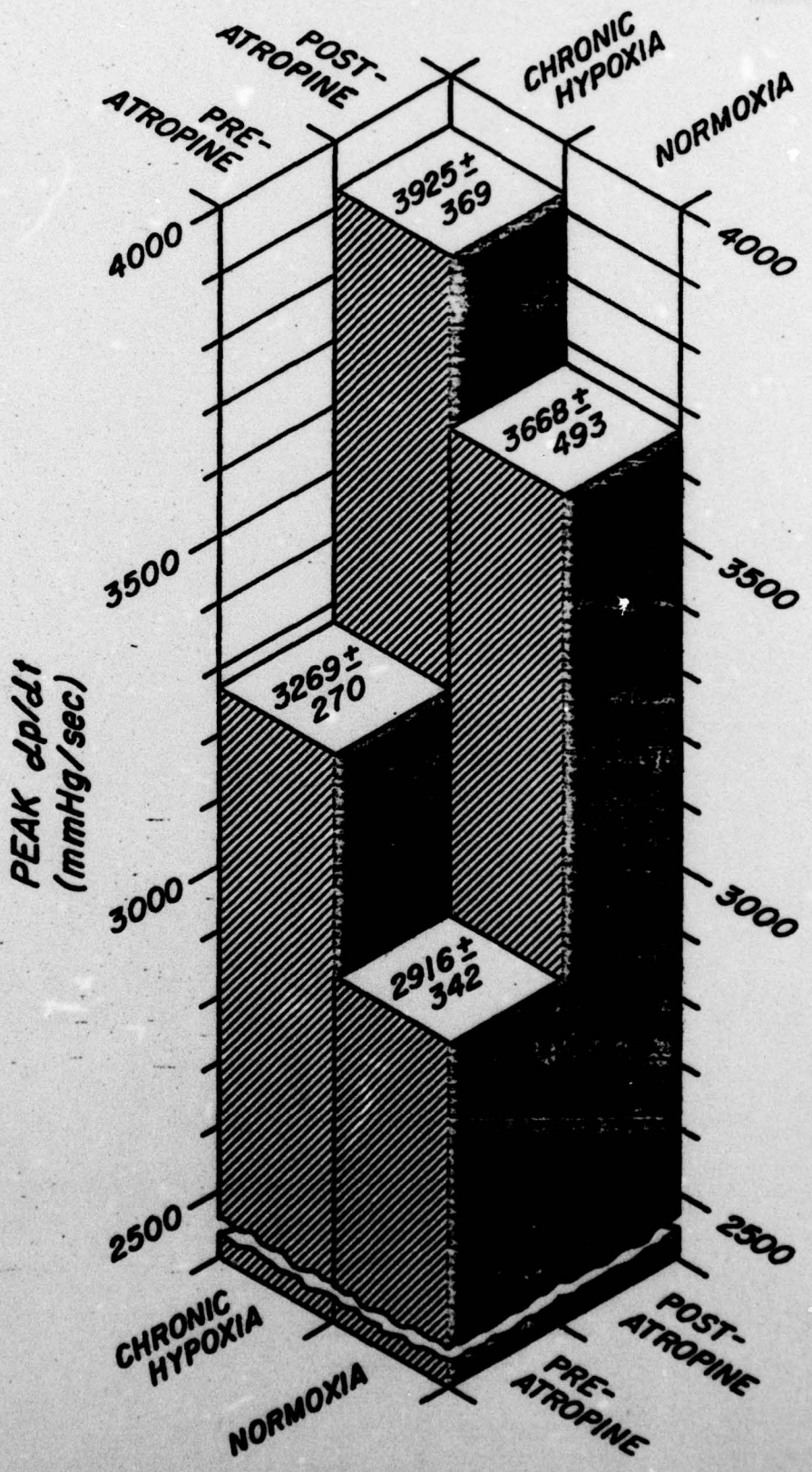

POST-ATROPINE
PRE-ATROPINE
CHRONIC HYPOXIA
NORMOXIA
160
140
120
100
HEART RATE (beats/min)
147±6
151±10
117±1
102±9
CHRONIC HYPOXIA
NORMOXIA
POST-ATROPINE
PRE-ATROPINE

Fig. 2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CHRONIC HYPOXIA
PRE-ATROPINE
NORMOXIA
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3500
3000
2500
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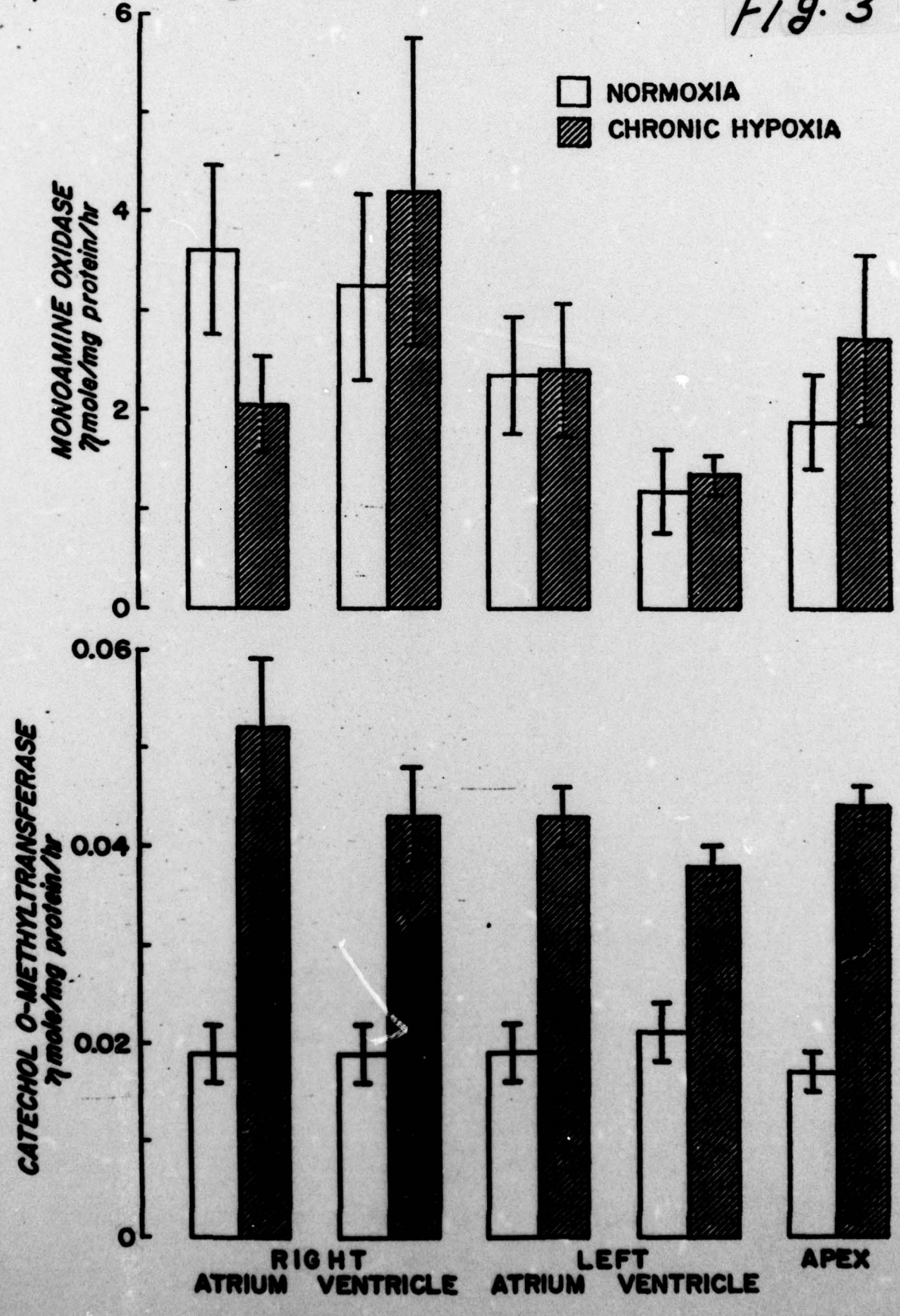
2916 ± 342
CHRONIC HYPOXIA
NORMOXIA
POST-ATROPINE
PRE-ATROPINE

Fig. 3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4
2
0
CATECHOL O-METHYLTRANSFERASE
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RIGHT
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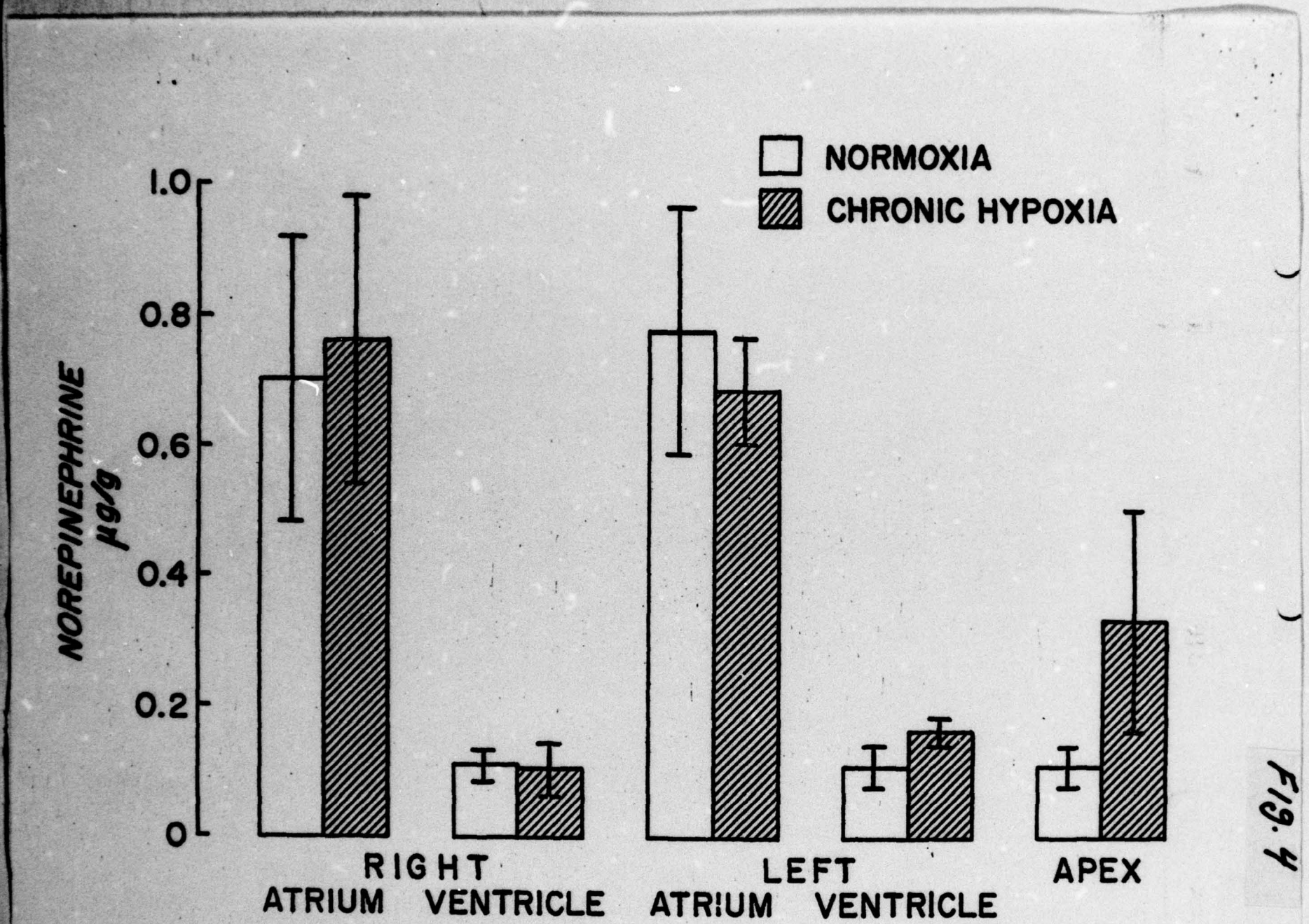
VENTRICLE
APEX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CHRONIC HYPOXIA
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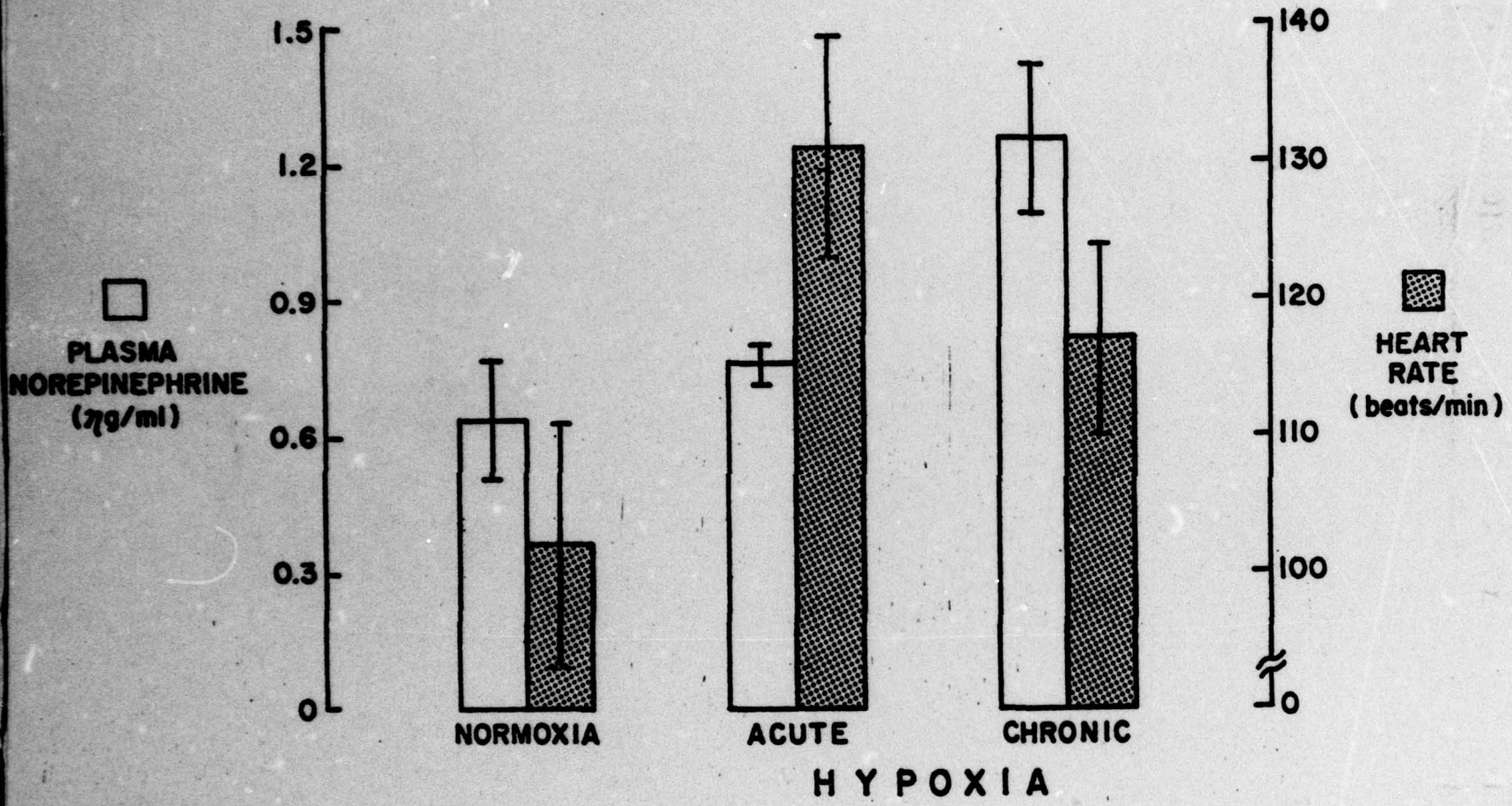
0.2
0
RIGHT ATRIUM
VENTRICLE
LEFT ATRIUM
VENTRICLE
APEX

Fig. 4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1.2
0.9
0.6
0.3
0
NORMOXIA
ACUTE
CHRONIC
HYPOXIA
140
130
120
110
100
0
HEART RATE (beats/min)

Fig. 5

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(14) REPORT DOCUMENTATION PAGE

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4. TITLE (and Subtitle): (6) MECHANISM OF THE ATTENUATED CARDIAC RESPONSE TO BETA-ADRENERGIC STIMULATION IN CHRONIC HYPOXIA,	5. TYPE OF REPORT & PERIOD COVERED / 6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s): (10) John T./ Maher, Joseph C./ Denniston, Danney L. / Wolfe[redacted] Allen/ Cymerman	8. CONTRACT OR GRANT NUMBER(s)
9. PERFORMING ORGANIZATION NAME AND ADDRESS: Altitude Research Division, US Army Research Institute of Environmental Medicine, Natick, MA 01760	10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS: (16) 3E762777A845 74183051
11. CONTROLLING OFFICE NAME AND ADDRESS: US Army Medical Research & Development Command, Washington, DC 20314	(11) 12. REPORT DATE: 14 Oct [redacted] 77 (12) 22p. / 13. NUMBER OF PAGES: 20
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office): Same as 11. above	15. SECURITY CLASS. (of this report): unclassified / 15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

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19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

normoxia; hypobaric hypoxia; vagal blockade; catecholamine degradative enzymes; chronotropic and inotropic responses

20. ABSTRACT (Continue on reverse side if necessary and identify by block number) A blunting of the chronotropic and inotropic responses of the heart to β-adrenergic stimulation occurs following chronic exposure to hypobaric hypoxia. To pursue the mechanism(s) involved, observations were made in 6 intact, conscious goats at sea level and in another 6 goats maintained in a decompression chamber at 445 torr (~4,300 m) for 10 days (P_aO_2 = 43 torr). No significant group differences in cardiac frequency and various indices of myocardial performance (peak dP/dt, time-to-peak dP/dt, V_{max}) were demonstrable either before or after cholinergic blockade with

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intravenous atropine methyl bromide, 1 mg/kg. Following hemodynamic studies, thoracotomies were performed and full-thickness biopsies were obtained from the free wall of each of the cardiac chambers. Neither monoamine oxidase activity nor norepinephrine level of any region of the heart was altered by chronic hypoxia. However, a twofold increase ($P < .001$) in catechol O-methyl-transferase activity above sea-level values was found in both the atria and ventricles of the hypoxic animals. Thus, the attenuation in cardiac responsiveness to β-adrenoceptor stimulation in chronic hypoxia appears unrelated to the level of vagal activity, but may be attributable to enhanced enzymatic inactivation of catecholamines.